The Egyptian Journal of Critical Care Medicine (2015) 3, 23–27

The Egyptian College of Critical Care Physicians

The Egyptian Journal of Critical Care Medicine

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ORIGINAL ARTICLE

Aspirin resistance: Prevalence and clinical outcome in Egypt

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Received 11 September 2014; revised 26 November 2014; accepted 26 December 2014
Available online 7 January 2015

KEYWORDS

Aspirin resistance;
Coronary artery disease;
Clinical outcome

Abstract *Introduction:* The antiplatelet drug aspirin is considered as a cornerstone in medical treatment of patients with CV or cerebrovascular diseases. Despite its use, a significant number of patients had recurrent adverse ischemic events. Inter-individual variability of platelet aggregation in response to aspirin may be an explanation for some of these events. Multiple trials have linked aspirin resistance to these adverse events.

Objectives: The aim of this study was to estimate the prevalence of aspirin resistance among patients with coronary artery disease (CAD) in Egypt and evaluate its impact on clinical outcome.

Methods: A total of 50 patients with documented history of CAD were included; they were on aspirin 150 mg/day for more than seven days and no other antiplatelet drugs. They were evaluated for aspirin resistance using light transmission aggregometry. Aspirin resistance was defined as a mean aggregation of >20% with 0.5 mg/ml arachidonic acid. They were followed up after six months for cardiac death, unstable angina (UA), myocardial infarction (MI), and stroke.

Results: Prevalence of aspirin resistance was 48% in our study group. Aspirin resistance was significantly higher in patients with family history of CAD ($p = 0.044$), smoking ($p = 0.011$), history of MI ($p = 0.024$), history of percutaneous coronary intervention (PCI) ($p = 0.001$), and concomitant NSAIDs intake ($p = 0.047$). Moreover, aspirin resistance was more common among patients with multi-vessel CAD ($p = 0.024$). Aspirin-resistant patients had a significantly higher rate of UA ($p = 0.001$) and all major adverse cardiac events (MACE) ($p < 0.001$).

1. Introduction

Atherothrombosis has long been recognized as a key contributor to cardiovascular (CV) events such as myocardial infarction (MI), unstable angina (UA), stroke, and transient ischemic attack (TIA). Given the important role of platelets in acute thrombus formation, antiplatelet therapies have become one of the cornerstone treatments of these atherothrombotic syndromes.

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Peer review under responsibility of The Egyptian College of Critical Care Physicians.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.ejccm.2014.12.001

In 1897, Felix Hoffman first developed acetylsalicylic acid and registered it under the name aspirin [1]. Aspirin specifically inhibits thromboxane (TX) A2 generation by irreversibly acetylating a serine residue at position 529 of the cyclooxygenase-1 (COX-1) enzyme [2].

The Antiplatelet Trialists Collaboration has shown a 25% reduction in strokes, MI, and CV deaths with the use of aspirin. However, aspirin has been shown to have variable antiplatelet effect in individual patients [3]. Incidence of treatment failure occurs with any drug and aspirin is not an exception, raising the possibility of aspirin resistance [4,5]. Aspirin resistance has been associated with adverse clinical events, increasing both morbidity and mortality [6–11].

2. Patients and methods

The protocol of this study was reviewed and approved by the Local Institutional Ethics Committee of Critical Care Department, Faculty of Medicine, Cairo University, Egypt.

Additionally, written informed consent entailing all moral and ethical consideration was obtained from all the patients participating in the study.

2.1. Patients

Our study was conducted prospectively on patients admitted to Critical Care Department, Faculty of Medicine, Cairo University, in the period from December 2009 to December 2010. The patients included in the study had a documented history of coronary artery disease (CAD) such as UA, MI, percutaneous coronary intervention (PCI), and/or coronary artery bypass graft surgery (CABG). Patients were excluded from the study on the basis of the following reasons: (1) administration of unfractionated heparin or low-molecular-weight heparin LMWH in the last 24 h before platelet aggregation testing, (2) personal history of bleeding disorders, (3) history of myeloproliferative disorder, (4) major surgical procedure in the last one week, (5) platelet count less than $150 * 10^9$/L or more than $450 * 10^9$/L.

Based on the above criteria, 50 patients were included for the study. Of the total selected patients, 30 (60%) patients were male, 35 (70%) were hypertensive, 25 (50%) were diabetic, 19 (38%) were smokers, 23 (46%) were obese, 27 (54%) had a family history of CAD, 13 (26%) had a history of MI, and nine (18%) had a history of PCI.

All patients were maintained on aspirin (150 mg/day) for more than seven days. No other antiplatelet therapies were implemented for their treatment.

2.2. Platelet function testing

Three samples of whole blood were collected in 3.8% sodium citrate (blue capped tube). The last dose of aspirin was administered within 1–24 h before sampling.

Blood samples were processed within two hrs of blood collection. Whole-blood specimens were centrifuged for 10 min at 120 g to obtain platelet-rich plasma (PRP). Platelet aggregation was performed on CHRONO-LOG platelet aggregometer (Chrono-Log Corporation, Havertown, USA) using the agonist arachidonic acid (AA) at 0.5 mg/ml. The tube containing platelet-rich plasma (PRP) was inserted in the aggregometer between a light source and a photocell, and then the agonist was added. When the platelets started to aggregate, the light transmission increased, which was directly proportional to the percent of platelet aggregation. Aspirin resistance was defined as a mean aggregation of $>20\%$ with 0.5 mg/ml AA.

2.3. Clinical follow up and study endpoints

In-hospital and post-discharge (after six months) follow-up data were prospectively collected. Compliance to medical treatment including aspirin was addressed. The study endpoints were CV death, UA, MI, and non-hemorrhagic cerebrovascular strokes. Other clinical events in the selected patients were assessed on the basis of phone interviews, outpatient follow up, and the information gathered from the hospital readmission records.

2.4. Statistical analysis

Data were statistically analyzed and presented as descriptive statistics, such as mean ± standard deviation (SD), frequencies (number of cases), and percentages, etc.

Comparison of numerical variables was done using Student's t test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used when the expected frequency was less than 5. Accuracy was represented using the terms sensitivity and specificity.

For our study, p values less than 0.05 were considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results

3.1. Prevalence of aspirin resistance

On the basis of the results of light transmission aggregometry, the patients were classified into aspirin sensitive (26/50; 52%) and aspirin resistant (24/50; 48%) as shown in Fig. 1.

3.2. Predictors of aspirin resistance

As shown in Table 1, aspirin resistance was found to be significantly higher in patients with a family history of CAD (70.8% vs. 38.5%, $p = 0.044$), smoking (58.3% vs. 19.2%, $p = 0.011$), MI (41.7% vs. 11.5%, $p = 0.024$), PCI (37.5% vs. 0%, $p = 0.001$), and concomitant non-steroidal anti-inflammatory

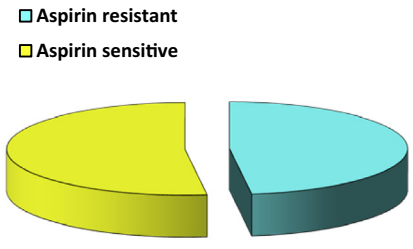

Figure 1 Prevalence of aspirin resistance.

Table 1 Predictors of aspirin resistance.

	Aspirin sensitive (No. = 26)	Aspirin resistant (No. = 24)	*p* Value
Mean age (years)	58.35 ± 5.05	55.54 ± 10.77	0.253
Male gender	16	14	1
Family history of CAD	10	17	0.044*
Current/recent smoking (<1Y)	5	14	0.011*
BMI >25	10	13	0.407
HTN	15	20	0.067
DM	14	11	0.777
Dyslipidemia	12	11	1
History of MI	3	10	0.024*
History of PCI	0	9	0.001*
Heart failure	4	8	0.11
PVD	0	1	0.48
History of CVS	2	1	1
Medications			
NSAID intake	3	9	0.047*
Nitrates	22	20	1
ACEI/ARBs	14	11	0.777
B-blockers	23	17	0.164
Statins	9	14	0.162
Diuretics	6	7	0.867
CCBs	2	4	0.409
Presentation			
Stable angina	16	11	0.256
UA	6	10	
Heart failure	2	3	
Angina equivalent	2	0	

CAD = Coronary artery disease, BMI = body mass index, HTN = hypertension, DM = diabetes mellitus, MI = myocardial infarction, PCI = percutaneous intervention, PVD = peripheral vascular disease, CVS = cerebrovascular strokes, NSAIDs = non steroidal anti-inflammatory drugs, ACEI = angiotensin converting enzyme inhibitor, ARBs = angiotensin receptor blocker, CCBs = calcium channel blockers.

* Statistically significant.

drug (NSAIDs) intake (37.5% vs. 11.5%, $p = 0.047$). Moreover, aspirin resistance was found to be more evident among patients with multi-vessel CAD (58.3% vs. 41.7%, $p = 0.024$) as shown in Fig. 2.

No statistical differences were observed for parameters like age, gender, BMI, diabetes, hypertension, and dyslipidemia ($p > 0.05$).

3.3. Study endpoints

No patients were lost to follow-up. In the aspirin sensitive group, 26 (100%) patients were event-free, while in the aspirin resistant group, 8 (33.3%) patients were presented with UA, one patient (4.2%) with ST segment elevation myocardial infarction (STEMI) and one patient (4.2%) with non-STEMI (NSTEMI). There were neither CV deaths nor cerebrovascular accidents (CVA) in both groups, as shown in Table 2.

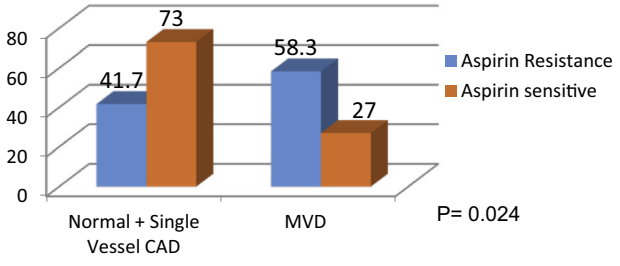

Figure 2 Coronary angiography result and aspirin resistance.

Table 2 Clinical outcome among the aspirin group.

	Aspirin responders (No. = 26)	Aspirin resistant (No. = 24)	*p* Value
Cardiac deaths	0	0	
Unstable angina	0	8 (33.3%)	0.001*
NSTEMI	0	1 (4.2%)	0.48
STEMI	0	1 (4.2%)	0.48
Non hemorrhagic CVA	0	0	
All MACE	0	10 (41.7%)	<0.001*

NSTEMI = non ST-segment elevation myocardial infarction, CVA = cerebrovascular accident, MACE = major adverse cardiac events.

* Statistically significant.

4. Discussion

Aspirin resistance is one of the important issues in current CV medicine. Antithrombotic Trialists' Collaboration provided evidence that 75–150 mg daily aspirin dosage is an effective method for secondary CV prevention [3]. Moreover, a significant number of patients do not get any benefit from aspirin monotherapy or even aspirin and clopidogrel dual therapy [12]. So, we initiated this study to estimate the prevalence of aspirin resistance in patients with CAD and to evaluate its impact on clinical outcome in our population.

In our study, the prevalence of aspirin resistance was noted to be 48%. This number was going parallel to other studies. Buchanan et al. [13] who studied 40 post-CABG patients treated with 325 mg of aspirin daily, found that approximately 42% of the patients were considered non-responders.

The Muller et al. [14] study also assessed 100 patients with peripheral vascular disease for aspirin resistance and showed a 60% incidence of aspirin resistance.

In another study, Gum et al. [15] studied 325 patients with stable coronary artery disease using optical platelet aggregometry and showed 5.5% incidence of aspirin resistance whereas 23% were aspirin semi-responders.

Various studies using different platelet function tests revealed estimates of aspirin resistance ranging from 5.5% to 60% [12]. This wide difference may be due to the difference in the dosage of aspirin, the method of defining resistance, type and concentration of the agonist used in testing, baseline platelet reactivity, and the type of population selected in the study (stable or unstable CAD, post CABG, post PCI, etc.).

Regarding predictors of aspirin resistance, we found that aspirin resistance was significantly higher in patients with a family history of CAD, history of MI, history of PCI, and concomitant NSAIDs intake. Also, aspirin resistance was significantly higher in patients who were current/recent smokers.

Similar to our results, Kojuri et al. [16] prospectively studied the effect of aspirin on platelet function in 106 stable outpatients. Six months after successful PCI, they observed that smoking ($p = 0.04$) was strongly associated with aspirin resistance.

Other studies, including Catella-Lawson et al. and Kurth et al. [17,18], also found that aspirin resistance was significantly elevated in patients with concomitant NSAIDs intake.

NSAIDs (especially ibuprofen) may compete with aspirin for binding to a specific serine residue on COX-1 enzyme and can potentially interfere with the cardioprotective effect of aspirin [19,20]. Hence, in September 2006, the Food and Drug Administration issued a statement for the physicians to be minded of this interaction [21].

In our study, we found no association between the female gender and aspirin resistance ($p = 1$); however in the work of Chen et al. [22] there was a significantly higher incidence of female subjects in the aspirin-resistant group. In another systematic review and meta-analysis of 20 studies that included 2930 patients with CV disease, aspirin resistance was found to be less prevalent in men than in women ($p < 0.001$) [23].

The same result was observed by Al-Azzam et al. [24] who studied 418 patients taking aspirin. The data collected in their research showed that aspirin resistance was not related to parameters, such as glycated hemoglobin (HbA1c), low-density lipoproteins (LDL), hypertension, age, and BMI, but was associated with the female gender ($p < 0.05$).

The difference between these results and the result obtained in our study may be attributed to the limited number of females enrolled (20 females).

In our study, aspirin resistance was found to be more prevalent in patients with multi-vessel CAD. However, in the study of Hobikoglu et al. [25], there were no significant differences in angiographic severity and the extent of coronary artery disease between the aspirin-resistant and aspirin-sensitive patients.

Many studies demonstrated the association of adverse clinical events in patients with aspirin resistance as determined by different assays [6–8,14,22,23,26]. Our study extended these observations and provided further evidence on the clinical significance of aspirin resistance as aspirin non-responders had a significant higher rate of UA ($p = 0.001$) and all major adverse cardiac events (MACE) ($p < 0.001$).

Our study had several potential limitations: (1) The study population was small, so important trends may not be identified because of a lack of statistical significance. (2) The antiplatelet effect may fluctuate in patients at the same dosage, so multiple measurements may be required to reflect the extent of platelet inhibition over a long period of time. (3) The lack of standardized timing between aspirin administration and blood sampling which is important, because the platelet inhibitory effect of aspirin declines through the usual 24-h interval [27]. (4) The study findings may not be extrapolated to other studies, since platelet aggregometry results obtained with different platelet aggregation tests do not correlate particularly well [28].

5. Conclusion

Prevalence of aspirin resistance among patients included in this study was 48%. Possible predictors of aspirin resistance included family history of CAD, history of MI, history of PCI, current/recent smoking, and concomitant NSAIDs intake. Aspirin resistance was more common among patients with multi-vessel CAD, and aspirin resistant patients had significantly higher rates of UA and MACE.

Recommendations

Larger, prospective, randomized and blinded studies are needed to accurately estimate the prevalence of antiplatelet resistance in our population, also possible treatment strategies and the role of platelet aggregation test in guiding antiplatelet therapy.

Conflict of interest

The authors declare no conflict of interests.

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